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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/977,865	10/15/2001	J Kevin Donahue	56495-2 (71699)	3724

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EXAMINER	
KATCHEVES, KONSTANTINA T	
ART UNIT	**PAPER NUMBER**
1636	

DATE MAILED: 02/25/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/977,865	DONAHUE ET AL.	
	Examiner	Art Unit	
	Konstantina Katcheves	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 July 2003 and 01 December 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,27,28,36-38,48-50,57-59,61,63,64,66 and 70-96* is/are pending in the application.

4a) Of the above claim(s) *27,28,36-38,48-50,57-59,61,63,64 and 66* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 70-96* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *19 February 2002* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claims 1, 27, 28, 36-38, 48-50, 57-59, 61, 63, 64, 66, and 70-96 are pending in the present application. Claims 27, 28, 36-38, 48-50, 57-59, 61, 63, 64 and 66 have been withdrawn from consideration. Claims 1 and 70-94 are under consideration. This Office action is in response to Applicant's papers filed 7 July 2003 and 1 December 2003.

Election/Restrictions

Applicant's election without traverse of Group I, claims 1 and 70-96 and elected species pyrazolo[4,3-d]pyrimidin-7-one and vascular endothelial growth factor (VEGF) in papers filed 7 July 2003 and 1 December 2003 is acknowledged. Claims 27, 28, 36-38, 48-50, 57-59, 61, 63, 64 and 66 withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in papers filed 7 July 2003 and 1 December 2003. Accordingly, claims 1 and 70-96 and elected species pyrazolo[4,3-d]pyrimidin-7-one and vascular endothelial growth factor (VEGF). Applicant should note that only sildenafil, not zaprinast and T-1032, will be searched as a member of the elected species, pyrazolo[4,3-d]pyrimidin-7-one, because it is the only phosphodiesterase (PDE) inhibitor of claim 73 having the elected core structure.

Priority

Applicant's claim for domestic priority under 35 U.S.C. 119(e) is acknowledged. However, the provisional application upon which priority is claimed fails to provide adequate

support under 35 U.S.C. 112 for claim 72 insofar as it reads on core structures other than pyrazolo[4,3-d]pyrimidin-7-one of this application.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1, 70, 74 and 96 rejected under 35 U.S.C. 102(b) as being anticipated by Goldring et al. (US Patent No. 5,516,651).

The invention of the instant claims is broadly drawn to a method comprising administering to cells a PDE inhibitor compound and an exogenous nucleic acid. In addition the cells are further exposed to a compound other than the PDE inhibitor.

Goldring et al. teach COS-M6 cells that are transfected with a construct and incubated in the presence of the PDE inhibitor, IBMX. The disclosure of Goldring et al. also teaches that the cells are incubated with a compound other than the PDE inhibitor, calcitonin (Column 9, lines 49-52).

Claims 1, 70, 74 and 96 are rejected under 35 U.S.C. 102(e) as being anticipated by Linden et al. (Pub. No. US 2002/0082240).

The invention of the present claims is relied upon as described above.

Linden et al. teach a method wherein genes are delivered to cells in the presence of a Type IV PDE inhibitor, rolipram. Moreover, the method comprises the administration of a compound other than a PDE inhibitor, an agonist of A_{2A} adenosine receptor (Page 12, claim 18).

Claim Rejections - 35 USC § 112

35 USC § 112, first paragraph - Written Description

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 70, 71, 72 and 96 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The written description requirement is established by 35 U.S.C. 112, first paragraph which states that the: "*specification* shall contain a written description of the invention. . .[emphasis added]." A specification must convey to one of skill in the art that "as of the filing date sought, [the inventor] was in possession of the invention." See *Vas Cath v. Mahurkar* 935 F.2d 1555, 1560 19 USPQ2d 1111, 1117 (Fed. Cir. 1991). Applicant may show that he is in "possession" of the invention claimed by describing the invention with all of its claimed limitations "by such descriptive means as words, structures, figures, diagrams, formulas, etc.,

that fully set forth the claimed invention." See *Lockwood v. American Airlines Inc.* 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (Fed. Cir. 1997).

The instant claims are drawn to bicyclic heterocyclic compounds as in claim 71 and pyrazolo[4,3-d]pyrimidin-7-one, as well as other core structures, in claim72. These claims are drawn to broad genuses of PDE inhibitor compounds having the claimed core structure, yet these core structures embrace a multitude of undefined modifications or constituents which increase nucleic acid uptake (Specification, page 5). Therefore, these are genus claims that encompass a wide array of molecules.

To adequately meet the written description requirement a claimed genus, must be described with "sufficient particularity such that one of skill in the art would recognize that the applicant had possession of the claimed invention." See MPEP 2163(I). The specification does not teach the essential or critical feature of bicyclic heterocyclic compounds and compounds having the core structures of clam 72. The specification only discloses sildenafil as a representative species, and it does not teach how sildenafil is representative of the broad genus of compounds embraced by the claims. The specification also fails to teach any essential or critical features of the claimed structures relate to the function of the genus. Thus, the specification does not describe the complete structure of a representative number of species.

Absent teachings and guidance as to the structure-function relationship of these compounds, the specification does not describe the claimed compounds in such full, clear, concise and exact terms so as to indicate that Applicant had possession of the invention at the time of filing of the present application. Thus, the written description requirement has not been satisfied.

35 USC § 112, first paragraph - Enablement

Claims 1 and 70-96 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for sildenafil, zaprinast and T-1032, does not reasonably provide enablement for any PDE inhibitor or any bicyclic heterocyclic compound or any compound having the core structure pyrazolo[4, 3-d]pyrimidin-7-one, pyrazolo[3,4-d]pyrimidin-4-one, quinazolin-4-one, purin-6-one, or pyrido[3,2-d]pyrimidin-4-one. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims. Applicant should note that this rejection is made in view of the scope of enablement rejection below. Therefore, for the reasons set forth in this rejection and the rejection set forth below, Applicant is enabled for sildenafil, zaprinast and T-1032 insofar as they relate to *ex vivo* and direct injection methods only.

The instant specification fails to provide information that would allow the skilled artisan to practice the instant invention without undue experimentation. Attention is directed to *In re Wands*, 8 USPQ2d 1400 (CAFC 1988) at 1404 where the court set forth the eight factors to consider when assessing if a disclosure would have required undue experimentation. Citing *Ex parte Forman*, 230 USPQ 546 (BdApls 1986) at 547 the court recited eight factors:

1) the quantity of experimentation necessary,

2) the amount of direction or guidance provided,

3) the presence of absence of working examples,

4) the nature of the invention,

5) the state of the prior art,

6) the relative skill of those in the art

7) the predictability of the art, and

8) the breadth of the claims.

The nature of the invention and breadth of the claims

The present invention is drawn to a method of administering nucleic acids to cells comprising treating the cell with a PDE inhibitor to increase nucleic acid uptake by cells. The present invention is broadly drawn to a large class of compounds these compounds include any that are PDE inhibitors, that are bicyclic heterocylic or that have one of the core structures pyrazolo[4, 3-d]pyrimidin-7-one, pyrazolo[3,4-d]pyrimidin-4-one, quinazolin-4-one, purin-6-one, or pyrido[3,2-d]pyrimidin-4-one. These claims include the addition of virtually any constituent to these core structures from a simple hydrogen group to ethyl, phenyl, alkyl, ether or methyl groups among many others.

The state of the art, skill of those in the art and predictability of the art

Many PDE inhibitors are known in the art indicated as therapeutics or potential therapeutics for a number of disorders. For example, sildenafil is a PDE-5 inhibitor and is also known by the trade name Viagra™. Sildenafil has been used to treat more than twenty million men with erectile dysfunction (Carson CC Sildenafil: a 4-year update in the treatment of 20 million erectile dysfunction patients, Curr. Urol. Rep. 2003 Dec.; 4(6) pp488-496) because of its properties as a vasodialator. PDE-4 inhibitors may be effective for chronic pulmonary disease, asthma and allergic diseases because they decrease inflammatory cell activity (Crocker I.C. therapeutic potential of phosphodiesterase 4 inhibitors in allergic diseases Drugs Today. 1999 Jul; 35(7): pp519-35 and DeKorte C.J. Current and emerging therapies for the management of

chronic inflammation in asthma Am J. Health Syst. Pharm. 2003 Oct. 1; (60)19: pp1949-59). PDE-3 inhibitors are thought to be involved in the treatment of obesity and diabetes. (Netherton S.J. et al. Altered PDE-e mediated cAMP hydrolysis contributes to a hypermotile phenotype in obese JCR:LA-cp rat aortic vascular smooth muscle cells: implications for diabetes associated cardiovascular disease. Diabetes. 2002 Apr; 51(4):1194-200). Each of these references is an example of the varied potential uses for PDE inhibitors. PDE inhibitors are known in the art to work on varied tissues to treat diseases that have different etiologies. Moreover, the different classes of PDE inhibitors have different mechanisms of actions such that one type would not necessarily work the same way another would. Thus, the use of any PDE inhibitor to increase nucleic acid uptake in cells is not necessarily predictable.

The quantity of experimentation necessary, the amount of direction or guidance provided, and the presence of absence of working examples

Applicant discloses a broad class of PDE inhibitors; however, the guidance and working examples provided in the specification are limited. Applicant teaches that sildenafil, zaprinast or T-1032 pretreatment of myocardial tissue *ex vivo* before VEGF exposure shows an increase in transfection efficiency of exogenous nucleic acids in the cells increased in comparison to VEGF alone. These data, however, do not teach one of skill in the art how to make and use each and every compound having the core structures above and each and every PDE inhibitor to increase exogenous nucleic acid uptake in cells.

Therefore, for the reason above, the nature of the invention, the lack of guidance and working examples in the specification, and the state of the art fail to sufficiently enable the full scope of the claimed invention.

Claims 1, 70-83, 84, 86-89, 91 and 93-96 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for *ex vivo* methods of nucleic acid delivery and direct injection of nucleic acids, does not reasonably provide enablement for all *in vivo* methods of delivery. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. Applicant should note that this rejection is made in view of the arguments set forth in the scope of enablement rejection above and the arguments found below. Therefore, for the reasons set forth in this rejection and the rejection set forth above, Applicant is enabled for *ex vivo* and direct injection methods only insofar as they are drawn to sildenafil, zaprinast and T-1032.

The instant specification fails to provide information that would allow the skilled artisan to practice the instant invention without undue experimentation. The relevant factors have been set forth above.

The nature of the invention and breadth of the claims

Methods of targeting nucleic acids into host cells *in vivo* fall into the broad area of gene therapy. Successful gene therapy methods are based, fundamentally, upon the ability to deliver exogenous nucleic acids to cells or tissues of interest. The invention of the instant claims is generally drawn to a method of gene therapy and is broadly drawn to a method of administering nucleic acids to the cells of tissues *in vivo* by administering the nucleic acid with a PDE inhibitor.

The state of the art, skill of those in the art and predictability of the art

Despite experimentation a tremendous amount of effort by skilled artisans in the field of gene delivery and expression *in vivo*, there remain significant hurdles known in the art to make and use the invention over the scope claimed. Anderson (Nature Vol. 392, supp 1998) reports that progress in developing effective gene therapy is slow. Anderson further states, "the efficiency of gene transfer and expression inhuman patients is, however, still disappointingly low. . . . [the] goal is more diffuclt to achieve than many investigators had predicted. . . [the] human body has spent many thousands of years learning to protect itself. . ." See page 25, column 1.

Verma et al. (Nature Vol. 389 1997), and Palu et al. (J. of Biotech. Vol.68 1999) also discuss the inherent difficulties transfecting cells *in vivo* by targeted delivery mechanisms. Transferred genes can be induced to function in a whole animal; however, no approach has been fully successful for *in vivo* gene transfer. See Verma page 239. Moreover, the main obstacle to the development of gene therapy is the targeted long-term expression of the transgene. The *in vivo* transfection of cells has not been fully successful for many reasons including the complexity the biological systems of living organisms, the inability of the genes to reach enough of the target cells, and the inability of the genes to function properly or for a significant period of time even if they do reach the cells. See Palu page 10 and Anderson page 25.

The quantity of experimentation necessary, the amount of direction or guidance provided, and the presence of absence of working examples

Applicant has not provided any working examples in the specification toward a method of administering nucleic acids to cells in a tissue of interest *in vivo*. Applicant only teaches that sildenafil, zaprinast or T-1032 pretreatment of myocardial tissue *ex vivo* before VEGF exposure shows an increase in transfection efficiency of exogenous nucleic acids in the cells increased in comparison to VEGF alone. These data, however, do not teach one of skill in the art how to direct the nucleic acid vector to its target location, deliver the nucleic acid to the target cell in a sufficient amount, or express the desired protein encoded by the nucleic acid properly.

In view of the factors above, the art of gene therapy and the art of gene delivery and expression is in its infancy and highly unpredictable. Therefore, the invention is not enabled for the full scope claimed by Applicant.

35 USC § 112, second paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 75 and 96 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 75 recites the limitation "that permeability agent." There is insufficient antecedent basis for this limitation in the claim. It is unclear to which agent the phrase "that permeability agent" refers.

Claim 96 recites the limitation "phosphodiesterase compound." Given the nature of the invention as set forth in the previous claims and the specification. It appears that this phrase should more appropriately recite "a phosphodiesterase inhibitor compound."

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Konstantina Katcheves whose telephone number is (571) 272-0768. The examiner can normally be reached on Monday, Tuesday, Thursday and Friday 7:30 to 5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Remy Yucel, Ph.D. can be reached on (571) 272-0781. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Konstantina Katcheves
February 23, 2004

JAMES KETTER
PRIMARY EXAMINER